Notice of Allowability	Application No.	Applicant(s)	
	09/344,189	ROGLER, CHARLES E.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the amendment received on 6/26/03*.

2. ☒ The allowed claim(s) is/are *54-99 (renumbered as 1-46)*.

3. ☒ The drawings filed on *26 June 2003* are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *0304* .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Mitchell Bernstein on 3/19/04.

The specification has been amended as follows:

In the claims:

Claims 1-53 have been cancelled. New claims 54-99 have been added as follows:

54. A method of making a chimeric mouse, comprising:

a) creating an immunetolerant mouse lacking functional T and B cells and having a genome which comprises a urokinase-type plasminogen activator (uPA) gene, expression of said uPA gene resulting in liver degeneration;

b) repopulating the parenchyma of the degenerated liver by transplanting xenogenic mammalian hepatocytes that are a natural host for infection with one or more compatible hepatitis virus into said liver; and

c) infecting the xenogenic mammalian hepatocytes with said one or more compatible hepatitis virus, said one or more compatible hepatitis virus selected

from the group consisting of mammalian hepatitis A virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus and hepadnavirus,

thereby making said chimeric mouse.

55. The method of claim 54, which comprises infecting the xenogenic mammalian hepatocytes with hepatitis virus prior to said transplanting.

56. The method of claim 54, which comprises infecting the xenogenic mammalian hepatocytes with hepatitis virus following said repopulation.

57. The method of claim 54, wherein the xenogenic mammalian hepatocytes are selected from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

58. The method of claim 47, wherein the xenogenic mammalian hepatocytes are human hepatocytes and the compatible mammalian hepatitis virus is human hepatitis B virus.

59. The method of claim 54, wherein the immunetolerant mouse which has a degenerated liver is created by:

a) crossing a hemizygous or homozygous urokinase-type plasminogen activator (uPA) transgenic mouse with a homozygous Recombination Activation Gene 2

(RAG-2) knockout mouse to generate F1 uPA hemizygous, RAG-2 hemizygous sibling mice; and

b) crossing the F1 mouse to another sibling F1 mouse or to a RAG2 homozygous mouse to generate a uPA hemizygous or homozygous, RAG2 homozygous (uPA/RAG2) F2 mouse.

60. The method of claim 59, wherein the xenogenic mammalian hepatocytes are from a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

61. A chimeric mouse model system for hepatitis comprising:

an immunetolerant mouse lacking functional T and B cells,

said immunetolerant mouse having a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant mouse, and said degenerated liver being repopulated with transplanted xenogenic mammalian hepatocytes that are infected with at least one compatible mammalian hepatitis virus, and

said at least one compatible mammalian hepatitis virus is selected from the group consisting of hepatitis A virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus and hepadnavirus.

62. The chimeric mouse model system of claim 61, wherein the xenogenic mammalian hepatocytes are infected with hepatitis virus prior to said transplantation.

63. The chimeric mouse model system of claim 61, wherein the xenogenic mammalian hepatocytes are infected with hepatitis virus following said repopulation.

64. The chimeric mouse model system of claim 61, wherein the xenogenic mammalian hepatocytes are selected from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

65. The chimeric mouse model system of claim 64, wherein the xenogenic mammalian hepatocytes are human hepatocytes and the compatible mammalian hepatitis virus is hepatitis B virus.

66. The chimeric mouse model system of claim 61, wherein the immunetolerant mouse having degenerated liver parenchyma is hemizygous or homozygous for said urokinase-type plasminogen activator (uPA) gene and is homozygous for a Recombination Activation Gene 2 (RAG-2) knockout mutation.

67. The chimeric mouse model system of claim 66, wherein the source of the xenogenic mammalian hepatocytes is a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

68. A method for screening a test compound for anti-viral activity, comprising:

a) administering said test compound to an immunetolerant chimeric mouse lacking functional T and B cells which has a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant chimeric mouse, said degenerated liver being repopulated with transplanted xenogenic mammalian hepatocytes that are infected with at least one compatible mammalian hepatitis virus selected from the group consisting of hepatitis A virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus and hepadnavirus; and

b) assaying the level of replication of the virus;

thereby screening said test compound for anti-viral activity.

69. The method of claim 68, wherein the mammalian hepatitis virus is hepatitis B virus.

70. The method of claim 68, which comprises comparing the level of viral replication in said mouse and in a control mouse which has not been administered the test compound.

71. The method of claim 68, wherein the xenogenic mammalian hepatocytes were infected with the compatible mammalian hepatitis virus prior to said transplanting.

72. The method of claim 69, wherein the xenogenic mammalian hepatocytes were infected with the compatible mammalian hepatitis virus following said repopulating step.

73. The method of claim 68, which comprises selecting the xenogenic mammalian hepatocytes from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

74. The method of claim 73, wherein the xenogenic mammalian hepatocytes are human hepatocytes and the compatible mammalian virus is hepatitis B virus.

75. The method of claim 68, wherein the immunetolerant mouse which has a degenerated liver is hemizygous or homozygous for said urokinase-type plasminogen activator (uPA) gene and homozygous for a Recombination Activation Gene 2 (RAG-2) knockout mutation.

76. The method of claim 75, wherein the source of the xenogenic mammalian hepatocytes is a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

77. The method of claim 68, wherein the antiviral compound is a member selected from the group consisting of interferons, cytokines, interleukins, growth factors, hormones, nucleoside analogues, and antisense DNA/RNA.

78. A method for screening a test compound for anti-cancer activity, comprising:

a) administering said test compound to immunetolerant chimeric mice lacking functional T and B cells,

said mice having a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant chimeric mice,

said degenerated liver parenchyma being repopulated with transplanted xenogenic mammalian hepatocytes that are infected with at least one compatible mammalian hepatitis virus capable of causing hepatocellular carcinoma in said xenogenic hepatocytes,

where said at least one compatible mammalian hepatitis virus is selected from the group consisting of hepatitis A virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus and hepadnavirus;

b) assaying said mice for the development of hepatocellular carcinoma virus; and

c) comparing the assay in the chimeric mice with the same assay carried out in control mice which have not been administered the test compound,

wherein the chimeric mice have precancerous or malignant cancerous hepatic tissue and wherein the development of hepatocellular carcinomas is assayed by monitoring for the prevention of the development of cancerous tissue from precancerous tissue or the amelioration of the malignant cancerous tissue,

thereby screening said test compound for anti-cancer activity.

79. The method of claim 78, which comprises comparing the presence of unique viral DNA integrations in the livers of said mice and in control mice which have not been administered the test compound.

80. The method of claim 78, wherein the xenogenic mammalian hepatocytes were infected with a hepatitis virus prior to said transplantation step.

81. The method of claim 78, wherein the xenogenic mammalian hepatocytes were infected with hepatitis virus following said repopulating step.

82. The method of claim 78, wherein the xenogenic mammalian hepatocytes are selected from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrels and woodchuck hepatocytes.

83. The method of claim 82, wherein the xenogenic mammalian hepatocytes are human hepatocytes and the compatible mammalian hepatitis virus is hepatitis B virus.

84. The method of claim 78, wherein the immunetolerant mice which have a degenerated liver are hemizygous or homozygous for said urokinase-type plasminogen

activator (uPA) gene and homozygous for a Recombination Activation Gene 2 (RAG-2) knockout mutation.

85. The method of claim 83, wherein the source of the xenogenic mammalian hepatocytes is a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

86. The method of claim 78, wherein the anticancer compound is a member selected from the group consisting of interferons, cytokines, interleukins, growth factors, hormones, nucleoside analogues, and antisense DNA/RNA.

87. A method of making a chimeric mouse, comprising:

a) creating an immunetolerant mouse, said immunetolerant mouse having a degenerated liver due to expression of a urokinase-type plasminogen activator (uPA) gene and lacking functional T and B cells, said uPA gene being present in the genome of said immunetolerant mouse;

b) transplanting human hepatocytes having at least 80% viability by intrasplenic injection to repopulate the parenchyma of the degenerated liver; and

c) infecting said hepatocytes with one or more compatible hepatitis virus selected from the group consisting of hepatitis A virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus and hepadnavirus,

thereby making said chimeric mouse.

88. The method of claim 87, wherein said immunetolerant mouse is about 10-14 days old at the time of transplanting said human hepatocytes.

89. The method of claim 88, wherein the transplanted human hepatocytes reconstitute approximately 10% of the degenerated liver.

90. The method of claim 54, wherein said uPA gene encodes secreted uPA.

91. The chimeric mouse model system of claim 61, wherein said uPA gene encodes secreted uPA.

92. The method of claim 68, wherein said uPA gene encodes secreted uPA.

93. The method of claim 78, wherein said uPA gene encodes secreted uPA.

94. The method of claim 87, wherein said uPA gene encodes secreted uPA.

95. The method of claim 87, which comprises infecting said hepatocytes with hepatitis virus prior to said transplanting.

96. The method of claim 87, which comprises infecting said hepatocytes with hepatitis virus following said repopulation.

97. The method of claim 87, which comprises infecting said hepatocytes with hepatitis B virus.

98. A method of making a chimeric mouse, comprising:

a) creating an immunetolerant mouse lacking functional T and B cells and having a genome which comprises a urokinase-type plasminogen activator (uPA) gene, expression of said uPA gene resulting in liver degeneration;

b) repopulating the parenchyma of the degenerated liver by transplanting human hepatocytes into said liver; and

c) infecting said human hepatocytes with human hepatitis B virus, thereby making said chimeric mouse.

99. A chimeric mouse model system for hepatitis comprising:
an immunetolerant mouse lacking functional T and B cells,
said immunetolerant mouse having a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant mouse, and said degenerated liver being repopulated with transplanted human hepatocytes that are infected with human hepatitis B virus.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is (571) 272-0732. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at 571-272-0804. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Official Fax Center number is (703) 872-9306.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (571) 272-0532.

Peter Paras, Jr.

Art Unit 1632

PETER PARAS, JR.
PRIMARY EXAMINER